Organic Process Research & Development **2006**, *10,* 184–193

# *Highlights from the Patents*

## A Review of U.S. Patents in the Field of Organic Process Development Published during November and December 2005


### Summary

The 21 patents selected this time came from and original list containing 146 that is even fewer than the last review. Despite the restricted choice from which to select patents its is hoped that there are some of interest. An improved method of preparing an antiviral salt gives a higher purity product that removed the need for expensive chromatographic purification. A process to prepare halogenated arylamines uses nonprecious metal catalysts that improve yield and cost less than palladium catalysts used previously. An efficient method of making diazomethane has been developed that is intended for continuous generation and use of the reagent. It reduces the inventory of the material so that health and safety aspects are significantly improved. A novel aryl coupling reaction, using Ni phosphine catalysts, is applicable to benzonitriles that are not amenable to other coupling procedures. Several novel indanones are disclosed that are of interest in preparing Zr metallocenes compounds used as polymerisation catalysts. A new, more active form of the COX-2 inhibitor celecoxib has been produced. This is achieved by the use of polymers that inhibit crystallisation and maintain the amorphous form that has increased bioavailability. Similarly, a patent describes novel forms of another nonsteroidal antiinflammatory drug, meloxicam. A new process for the preparation of the antidepressant citalopram uses the same basic procedures as the original work with improvements in some stages. Insomniacs may be interested in the development of some novel chiral carbonates that are used to prepare zopiclone. These intermediates are obtained from racemic mixtures by resolution using immobilised enzymes. A new method is described to produce novel epoxy intermediates that are used to prepare α-lipoic acid. Both enantiomers of the acid are of interest since they each have different types of activity, and the new route can be used to prepare either. One patent claims to have developed a process for producing *N*-vinylformamide, a monomer used in the preparation of water-soluble polymers. However, the monomer was not isolated and its presence only shown by NMR. The increase in the use of colour printers may be behind the development of a method to prepare a range of dihydroxydiphenyl sulfones. The 2,4-isomers are used as colour developers for heat-sensitive paper, whereas the 4,4-isomers are not suitable. A base-catalyzed ring-closure reaction of acrylates using $Li_2CO_3$ has been used to obtain nicotinate esters for insecticides. This process is very effective and replaces the normal method of using NaOMe. The minimisation or complete removal of solvents is an important environmental subject and is covered in one patent. This is done by using poly(ethylene glycol) ethers that behave in a manner similar to that of crown ethers, solubilising the metal compounds by complex formation. The patent describes several reactions using these ethers that do not use solvents. On another environmental topic a safe replacement for CFCs could be $CF_3I$, and a new one-step process for its production is described. The deliberate production of agglomerates during crystallisation is described by modification of the mixing method used in the process. This technique is then applied to the production of antibiotic formulations. There is no legal or commercial significance to the patents selected here, and the advantages given are those claimed in the patent unless this reviewer has personal knowledge of the subject. Several of the patents give details indicating that the work has been carried out at a lager scale than laboratory tests. This may indicate the process is at an advanced commercial stage. On the other hand some patents claim commercial utility without giving any evidence to support this.


### Patent No. U.S. 6,960,668

***Assignee: Great Lakes (UK) Limited, Cheshire, United Kingdom***

***Title or Subject: Process for the Production of Substituted Thioxanthones***

The compounds such as **3a**−**c** that contain side chains with reactive groups are used as intermediates in the pharmaceutical and photochemical industries. Specific isomers are usually desired, and most synthetic routes produce mixtures of isomers such as **3** or **4** and give low overall yields because several steps are required. This patent provides a one-step process outlined in Scheme 1 in which a substituted benzoic acid such as **1** is reacted with a phenoxyacetic acid (**2a**−**2c**) in the presence of $H_2SO_4$. After reaction the mixture is quenched with water, and the products obtained are the isomers **3a**−**3c**. For compound **3a** the assay by HPLC was >98%. If the reaction is carried out using the phenoxyacetic acid **2d**, then the product is **4**. This demonstrates that the electronic properties of the group at $R_1$ is dictating the final isomer obtained.


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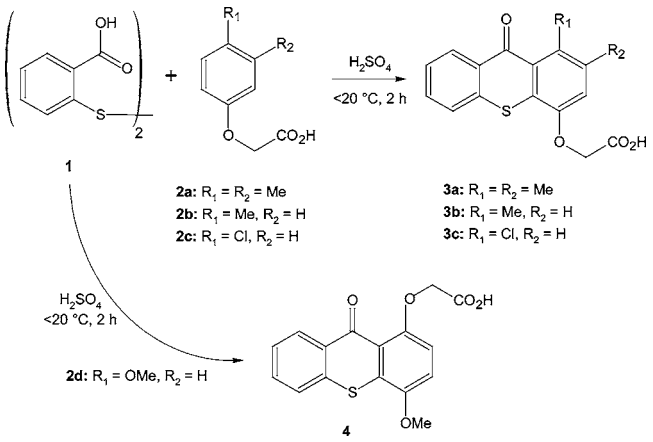
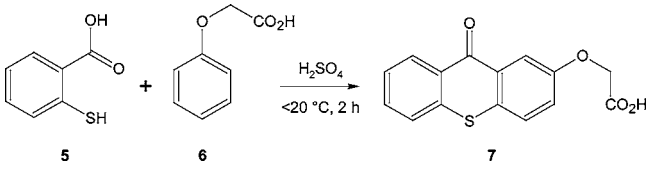
Scheme 1




The patent also describes the use of mercaptobenzoic acid **5** in the reaction with **6** to give **7** as shown in Scheme 2. Only the isomer **7** was obtained, and the HPLC assay was 97%.

Scheme 2




## Advantages

This fairly simple process does provide a method of obtaining the desired isomer without resort to multistep reactions.

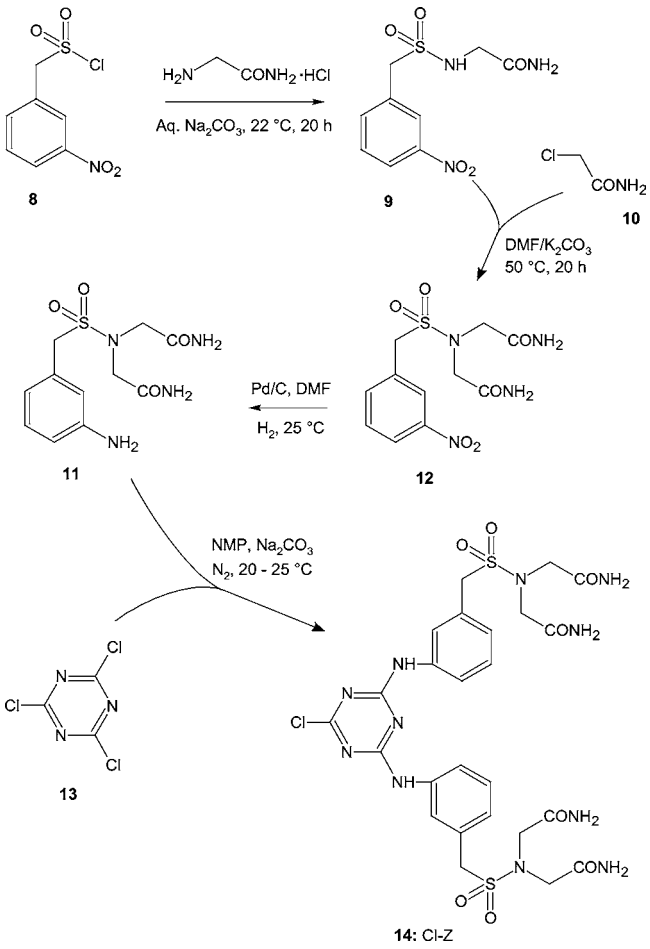
## Patent No. U.S. 6,960,686

### *Assignee: Wyeth, Madison, New Jersey, U.S.A.*

### *Title or Subject: Preparation and Purification of Antiviral Disulfonic Acid Disodium Salt*

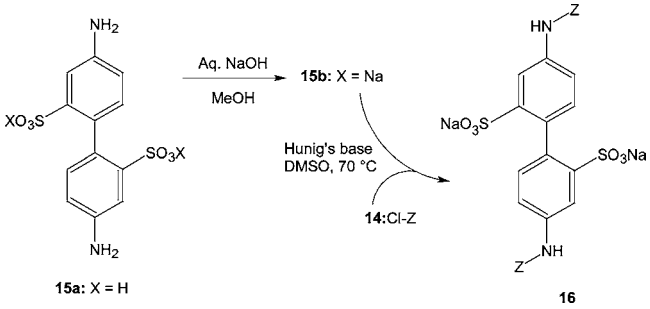
The salt **16** (Scheme 4) is used as an antiviral agent, and it is claimed that by using alternative synthetic procedures it is possible to obtain **16** at a maximum purity of 80%. This then requires extensive purification using chromatographic techniques. To achieve this level of purity it is said that reaction intermediates also require purification, and hence the overall yield of **16** is significantly reduced. The current patent describes a method for preparing **16** with a purity of >97% without using chromatography. The first stage in the synthesis is the preparation of the intermediate **14** by the route outlined in Scheme 3. This begins with the formation of **9** by reaction of **8** with the HCl salt of aminoglycine in basic solution. Treatment of **9** with **10** in basic solution gives the bisacetamide **12** that is easily reduced to the amino derivative **11**. The condensation of **11** with cyanuric chloride **13** has been reported elsewhere as taking place at 120 °C and requiring the use of a phosphate buffer. However, the patent describes that the reaction does take place without a buffer in NMP at much lower temperatures. The final product **14** is recrystallised from NMP/water.

Scheme 3




The final stage of the synthesis of **16** is shown in Scheme 4 and involves the condensation of **14** (Cl−Z) with the disodium salt **15b** in DMSO in the presence of Hunig's base. Previous reports indicate that this reaction is carried out at 120 °C, but it has been found that by using DMSO this is not necessary. At about 70 °C the reaction proceeds smoothly over a period of 96 h to give **16**, but the yield is poor and is only 37%. The use of lower temperatures results in fewer byproducts and makes purification easier.

Scheme 4




## Advantages

The process employs milder conditions for some reactions than alternative routes and as a result gives intermediates that are of higher purity. The use of these then allows the production of the final product that is of sufficiently high purity that extensive purification is not needed.

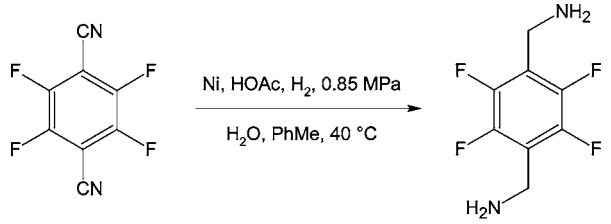
## Patent No. U.S. 6,960,691

***Assignee: Showa Denko K. K., Tokyo, Japan***

***Title or Subject: Production Process for Halogenated Aromatic Methylamine***

The main compound of interest in this patent is the diamine **18** that is used as an intermediate in the preparation of insecticides. A common method of preparing aromatic amines is by hydrogenation of nitriles in the presence of $NH_3$. However, this method is not successful if halogenated aryl compounds are involved and by-product *sec*-amines are formed by substitution of a halogen by an amino group. There are reports of methods to prevent these side reactions by carrying out the hydrogenation in acidic conditions. Unfortunately, a strong acid such as $H_2SO_4$ is used, and expensive Pd catalysts are needed since Ni or Co catalysts dissolve. The method disclosed in this patent uses the cheaper sponge Ni catalyst and the weaker acid HOAc in the production of **18** by hydrogenation of **17** (Scheme 5). The reaction is carried out in a two-phase solvent system of water and PhMe. The product is obtained in a yield of 83% with conversion of **17** of >99%.

Scheme 5




**17** **18**

### Advantages

The process allows the use of cheaper catalysts and gives higher yields than alternatives.

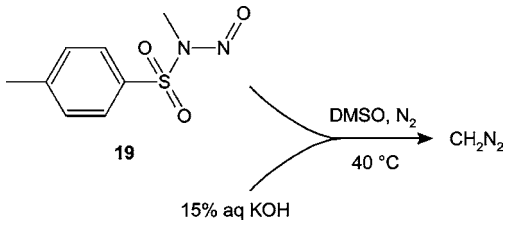
## Patent No. U.S. 6,962,983

***Assignee: Phoenix Chemicals Limited, Bromborough, United Kingdom***

***Title or Subject: Process for the Preparation of Diazomethane***

Diazomethane is an extremely useful but carcinogenic and dangerously explosive material. Hence, special techniques are required when it is used, and it is not easily stored. This patent describes a method for the generation of $CH_2N_2$ so that it is used as it is produced, and hence the total inventory in the equipment is very low. An article on this subject has been published recently (*Org. Process Res. Dev.* **2002**, *6*, 884). The $CH_2N_2$ is produced from the *N*-nitroso compound **19** by decomposition with aqueous KOH solution. The process involves pumping a solution of **19** in DMSO and solution of KOH into a reactor along with $N_2$ to sparge the $CH_2N_2$ from the reactor. The amount of $N_2$ is chosen so that the explosive limit of $CH_2N_2$ is not exceeded, and this equates to a concentration of $CH_2N_2$ of 14.7%. Any reaction of $CH_2N_2$ takes place in the reactor, and excess unreacted $CH_2N_2$ is quenched at the outlet of the reactor by passing the exit stream into HOAc. An important aspect of the procedure is to maintain laminar flow conditions inside the reactor.

Scheme 6




**19**

The patent does not give specific details of reactions in which the system is used, although diazoketone preparation is mentioned. The system described in the patent is capable of producing 652 kg of $CH_2N_2$ per year at 80% utilisation. By adjustment of the flow rates and reactor volume the system is said to be capable of producing 5−10 kg/h with a total inventory of $CH_2N_2$ of only 100 g.

### Advantages

This process is a safe method of forming and using the versatile reagent in large-scale production.

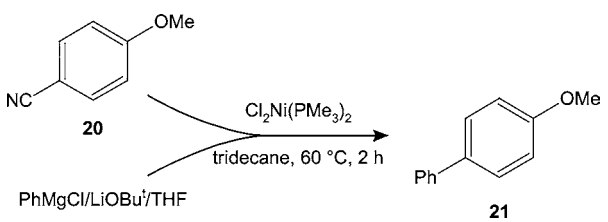
## Patent No. U.S. 6,962,999

***Assignee: Pharmacore Inc., High Point, North Carolina, U.S.A.***

***Title or Subject: Process for Preparing Unsymmetrical Biaryls and Alkylated Aromatic Compounds from Arylnitriles***

The coupling of aromatic compounds is a widely used reaction, and a number of methods are available involving organometallic reagents. There are a large number of alternative methods that can be used to couple many types of compounds, and these are summarised. However, the reactions are not applicable on a large scale to the coupling of benzonitriles when the nitrile group is displaced by the alkyl or aryl portion of the organometallic reagent. Scheme 7 shows the application of the method to prepare **21** from the nitrile **20** by using the Grignard reagent PhMgCl and $LiOBu^t$. The reaction can also be carried out using alternative Ni phosphine catalysts.

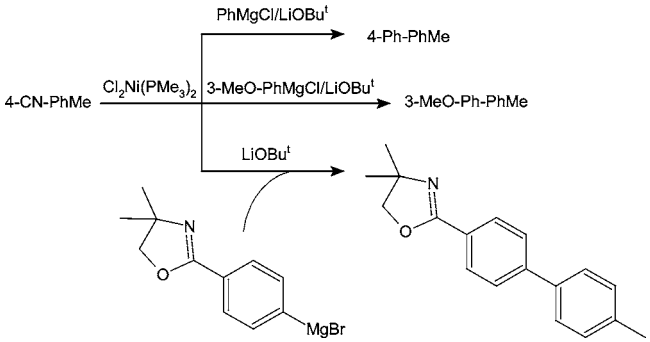
Scheme 7




**20** **21**

The method can also be used to prepare a range of other compounds from a variety of nitriles using the same Ni catalyst; a selection is shown in Scheme 8. There are other examples in the patent in which alternative catalysts, metal alkyls, or Li bases are used.

Scheme 8




## Advantages

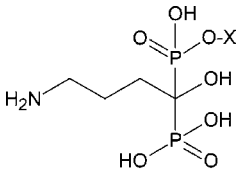
The facile method enables coupling of nitrile compounds that otherwise cannot be used in this type of reaction.

## Patent No. U.S. 6,963,008

### *Assignee: Teva Pharmaceutical Industries Ltd., Petah Tiqva, Israel*

### *Title or Subject: Processes for the Manufacture and Pharmaceutical Compositions of Novel Alendronate Sodium Hydrates*

The subject of this patent **22b** is used in treating bone diseases such as osteoporosis and Paget's disease. This patent describes new hydrate forms of **22b** having between 1.3 and 11.7% water. These water concentrations correspond to new crystalline hydrates having from $^1/_{14}$ to 2 molecules of water per molecule of **22b**. The hydrates are obtained from anhydrous acid **22a** that is converted to the anhydrous Na salt **22b**. The anhydrous Na salt is then heated with varying quantities of alcohols and NaOH to produce the different crystalline hydrates. The patent contains X-ray diffraction (XRD), IR, and thermogravimetic data for all hydrates.




**22a:** X = H
**22b:** X = Na

## Advantages

The new forms will extend the commercial opportunities of this drug.

## Patent No. U.S. 6,963,017

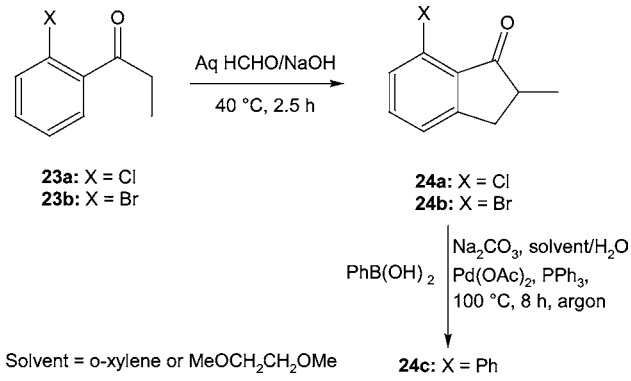
### *Assignee: Basell Polyolefin GmbH, Wesseling, Germany*

### *Title or Subject: Preparation of Substituted Indanones and their use in Preparing Metallocenes*

The compounds of interest in this patent are used in the preparation of metallocenes that are catalysts used in the manufacture of polyolefins. An earlier patent on this topic has been reviewed previously (*Org. Process Res. Dev.* **2005**, *9*, 719). The claims of this patent cover a very large number of novel indanone compounds.

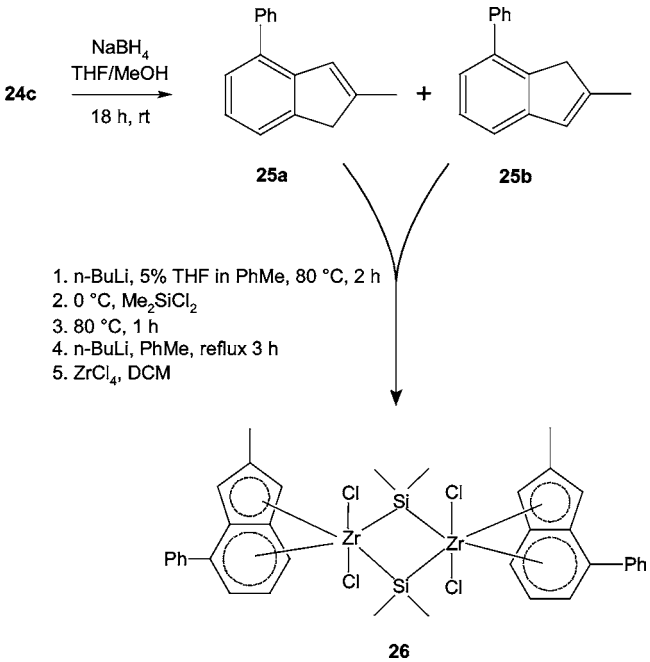
Scheme 9 summarises the method used to prepare halo-compounds **24a** and **24b** by reaction of the ketone **23a** or **23b** with HCHO. The halo compounds are subsequently used to prepare a range of derivatives such as **24c** by a Pd-catalysed coupling reaction using a variety of boric acid esters. The patent provides almost 60 examples of indanones and basic $^1$H NMR data are given for many of them.

Scheme 9




The indanones such are **24c** used to prepare Zr metallocenes such as **26**. The route used is shown in Scheme 10 and begins with the reduction of **24c** using $NaBH_4$ to give the indenes **25a** and **25b**. The patent does not indicate which isomer is produced or if a mixture is obtained, and in fact, in the second stage of the procedure it does not matter. However, it is reasonable to assume that this reduction is nonselective and both are obtained. The hydrogenation of **24c** presumably forms **25a** by reduction and then dehydration, and this is likely to isomerise to **25b**. The indenes **25a** and **25b** are then converted to the Li salt and treated with $Me_2SiCl_2$, followed by $ZrCl_4$, to give **26**. Several examples of similar zirconocenes to **26** are described in the patent, and basic $^1$H NMR data are provided.

Scheme 10




**26**

## Advantages

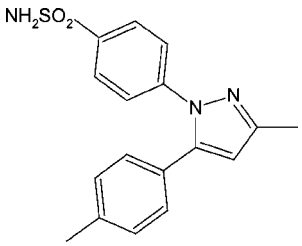
This process provides a route to a novel range of indanones that can be used to make highly active metallocene catalysts.

## Patent No. U.S. 6,964,978

***Assignee: Pharmacia Corporation, St. Louis, Missouri, U.S.A.***

***Title or Subject: Solid-State Form of Celecoxib Having Enhanced Bioavailability***

There have been many reports in both the scientific and nonscientific literature about COX-2 inhibitors that are nonsteroidal antiinflammatory agents. **27** is the active ingredient of the drug Celebrex, and this patent describes an amorphous form of **27** that improves the effectiveness of the drug. The patent describes drug formulations containing amorphous **27** and materials described as crystallisation inhibitors (CI). These are polymers that form a composite with **27** and prevent its conversion to crystalline forms that are less pharmaceutically active than the amorphous form. Examples of such polymers are poly(vinylpyrrolidone) and hydroxypropylmethylcellulose. The amorphous form of **27** is produced by spray-drying a solution of crystalline **27** and the CI in *i*-PrOH. The solid obtained is used to formulate the drug. XRD and differential scanning calorimeter (DSC) data are provided for the materials.




**27**

## Advantages

This process provides more active forms of known drug materials.

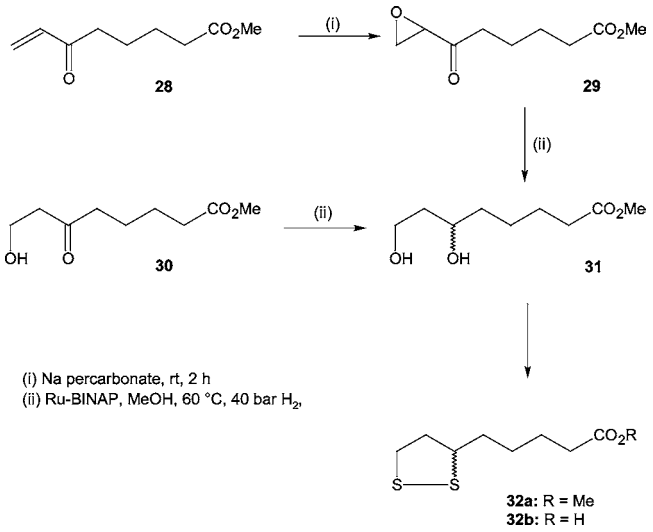
## Patent No. U.S. 6,965,029

***Assignee: Viatris GmbH & Co. KG., Frankfurt, Germany***

***Title or Subject: Method for Producing Enantiomer-Free 6,8-Dihydroxyoctanoic Acid Esters by Asymmetric, Catalytic Hydrogenation***

The main subject of this patent is the asymmetric hydrogenation of compounds **29** and **30** to give **31** that is an intermediate in the formation of α-lipoic acid **32b** (Scheme 11). **32b** occurs naturally in small concentrations in virtually all animal and vegetable cells and is pharmaceutically active. Each of the two enantiomers of **32** is of interest since they have different types of activity. There are synthetic routes to make **32b**, but these are said to be unattractive for commercial use. The catalysts used for the hydrogenation are Ru catalysts that contain a chiral phosphine ligand. The catalyst used in the examples is based on the BINAP ligand. Scheme 11 summarises the reaction sequence to form **32b**. The novel epoxy compound **29** is produced by oxidation of **28** using sodium percarbonate. Hydrogenation of either **29** or **30** gives **31** stereoselectively, and either enantiomer of **31** can be obtained by using the appropriate chiral phosphine. There are no examples describing the conversion of **31** to **32.** However, the patent claims do mention that this is via the bisulphonic acid ester of **31** followed by treatment of **31** with S and a metal sulphide to give the ester **32a**.

Scheme 11




The patent provides basic $^{13}C$ NMR data for the novel compounds **29**, **30**, and **31**. An example is also given that describes the oxidation of **31** to **30** using NaOCl. The hydrogenation of **29** to **30** using $PtO_2$ catalyst is also described.

## Advantages

The compound **28** is said to be commercially available, and hence this process provides a convenient method of producing **32b** from readily available sources.

## Patent No. U.S. 6,965,052

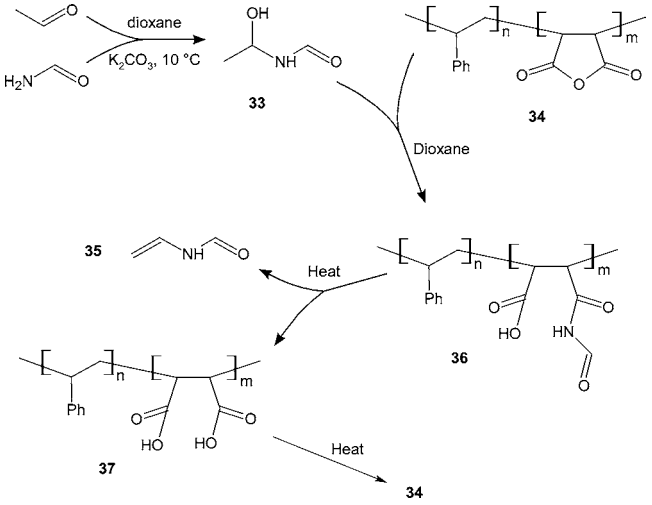
***Assignee: University of Pittsburgh, Pittsburgh, Pennsylvania, U.S.A. and SNF SA, Andreziux Cedex, France***

***Title or Subject: Synthesis of N-Vinylformamide***

The title compound (NVF) **35** is used to prepare polyNVF that is a water-soluble polymer. PolyNVF is said to be the most practical precursor to polyvinylamine since vinylamine is unstable. Polyvinylamine is a potentially less toxic alternative to polyacrylamide. Commercial routes to **35** are in operation and use either HCN or thermal cracking of hydroxyethyl formamide **33**. Clearly, handling HCN is very hazardous, and the routes using **33** do not give NVF with sufficiently high purity. This patent describes a new route to **35** from **33** that is shown in Scheme 12. The process produces **33** from MeCHO and $H_2NCHO$ in the presence of a styrene anhydride copolymer **34**. This reaction is carried out sequentially without isolation of **35** and produces **36** that is cracked to give **35** and the diacid polymer **37**. Dehydration of **37** by heating gives the anhydride **34** that can be reused.

The conditions for cracking the polymer **36** are suggested to be 150 °C at 2 mmHg. No details are provided, but it is claimed that this will produce **35** as a gas that can be condensed.

Scheme 12




The experimental details are limited; the product was not isolated, but its presence was confirmed by NMR. An alternative method using a tethered silylated anhydride is also mentioned, but again limited details are given.

### Advantages

The process could be an improvement on existing methods, but the limited details do not allow an assessment of this claim.

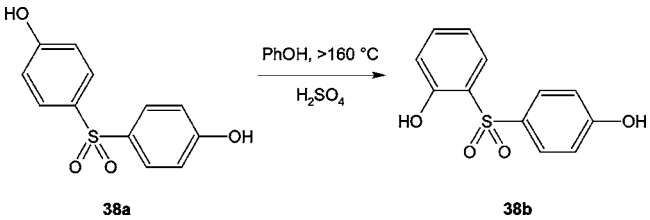
### Patent No. U.S. 6,965,054

***Assignee: Konishi Chemical Ind.Co., Ltd., Wakayama, Japan***

***Title or Subject: Process for Producing Mixture of Dihydroxydiphenyl sulfone Isomers***

The 2,4-isomer **38b** is of great interest as a colour developer for heat-sensitive paper. Processes for preparing **38b** also produce the 4,4-isomer **38a**, and hence, the two isomers need to be separated. Heating **38a** in a the presence of an acid does produce a mixture containing about 25% **38b** but this takes about 20 h at 190 °C for completion (Scheme 13). This patent discloses that by using specific amounts of $H_2SO_4$ in PhOH the isomerisation of **38a** to **38b** can be carried out more quickly. The process is carried out by heating a mixture of **38a** with no more than 50% phenol and no more than 20% of $H_2SO_4$ in the mixture. The temperature needed is >160 °C. At 195 °C **38a** containing 50 wt % PhOH and 4 mol % of $H_2SO_4$ gave a mixture containing 15% of **38b**; after 6 h this had increased to 24%. By increasing the temperature to 210 °C and the $H_2SO_4$ to 10 mol % the time to achieve equilibrium was reduced to 2 h.

Scheme 13




**38a** **38b**

### Advantages

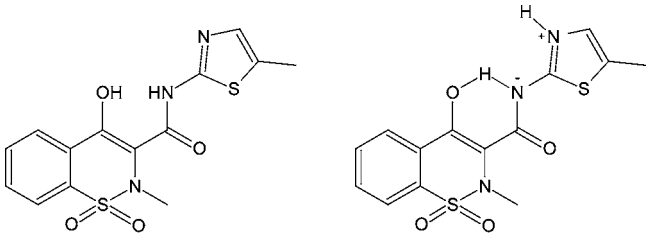
The process does significantly reduce the time for formation of the desired isomer but gives no indication as to how the separation is achieved.

### Patent No. U.S. 6,967,248

***Assignee: Esteve Quimica SA, Barcelona, Spain***

***Title or Subject: Processes for the Preparation and Interconversion of New Crystalline Forms of Meloxicam***

Meloxicam **39a** is a nonsteroidal antiinflammatory drug that exhibits polymorphism, and two crystalline forms are known. The enolic form **39a** is known as Form I and is used for pharmaceutical products; the second form is a zwitterion **39b** designated as Form IV in this patent. The current method for preparing **39a** is said to require the use of chlorinated solvents. This is not good practice, and the patent attempts to provide an improved procedure for preparing Form I. The patent describes methods for preparing pure Form I and discloses three new polymorphs designated Forms II, III, and V. It also describes how these new polymorphs may be converted to Form I.




**39a** **39b**

The preparation of the pure crystalline Form I is carried out by heating solutions of meloxicam in aqueous NaOH with or without EtOH, MeOH, or DMF. The procedures take place at various temperatures from 65 to 100 °C and are followed by acidification. Acids used include HOAc, HCl, and $MeSO_3H$. Variations on these procedures can produce the new forms of **39a**. XRD and Raman spectra for the new forms are provided in the patent.

### Advantages

The process gives an improved method of making the desired form of the drug and provides new polymorphs that may be used to prepare new formulations.

### Patent No. U.S. 6.967.259

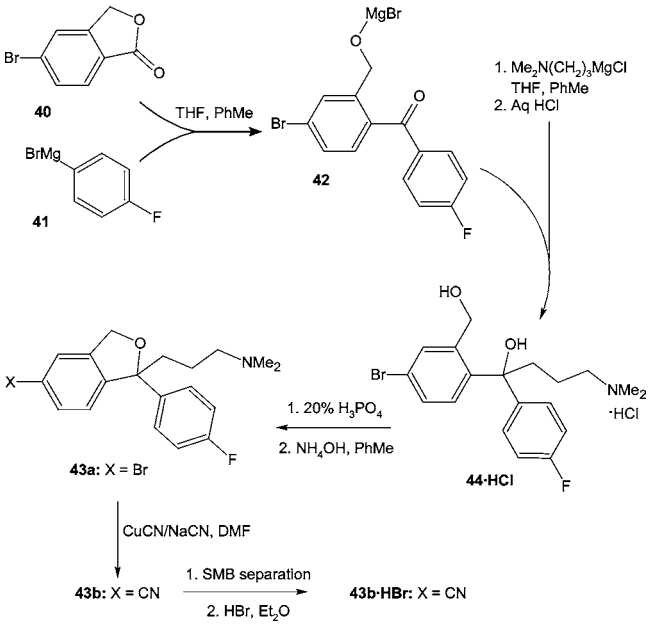
***Assignee: Pharmachem Technologies Limited, Bristol, United Kingdom***

***Title or Subject: Process for the Prepartion of Citalopram Intermediate***

Citalopram **43b** is an antidepressant that is used as a racemate in the HBr or oxalate salt form. There are several

process known for the synthesis of **43b**, and since the original patent has now expired, there is increased interest in new synthetic methods for this well-known drug. Scheme 14 shows the route used to produce **43b**·HBr. The synthetic route uses the same chemistry as that of the original patent with some minor differences in the use of reagents. For example, for the conversion of **44**·HCl to **43a** the process uses 20% $H_3PO_4$ rather than 60% as in the original patent. This is said to give a higher-purity product and to reduce the amount of $NH_3$ needed in the subsequent neutralisation step. In another change a mixture of NaCN and CuCN is used to produce **43b** from **43a** rather than only using CuCN. However, a major difference between this and the original patent is the use of simulated moving bed chromatography (SMB) to purify the free base **43b**. The major impurity is unreacted **43a** and is difficult to remove. Other impurities that are difficult to remove from **43b** are demethylated derivatives of **43b**. These are removed by treating the reaction mixture with a scavenger resin. An example given is polystyrene resin with a methylisocyanate group although the actual identity is not revealed.

Scheme 14




The patent also reports that the production of the intermediate salt **44**·HCl can give different polymorphs, depending upon the solvent used for recrystallisation. For example, using THF/PhMe gives one polymorph and *n*-BuOH gives another.

## Advantages

The process provides an alternative method of preparing this important drug now that the original patent has expired.

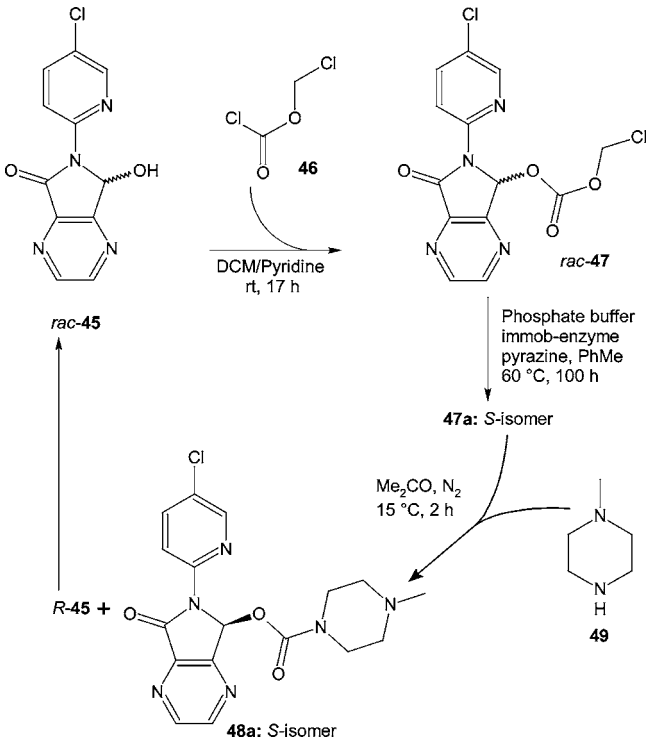
## Patent No. U.S. 6,969,767

***Assignee: Universidad De Oviedo, and Astur Pharma S. A. Both of Oviedo, Spain***

***Title or Subject: Optically Active Carbonates as Precursors of (+)-Zopiclone***

The racemate of zopiclone **48** is used to treat insomnia although the *R*-isomer is inactive and may cause some of the side effects of the drug. This patent provides a method of obtaining the active *S*-isomer **48a** and does so by a method involving the synthesis of some novel chiral intermediates such as **47a**. The route used is shown in Scheme 15 and begins with the condensation of **45** with the chloroformate **46** to give the racemic compound **rac-47**. The next stage is the resolution of **rac-47** using an immobilised enzyme that hydrolyses the *R*-isomer to *R*-**45** and leaves the pure *S*-isomer. In this step the *R*-**45** actually spontaneously racemises to give racemic **45** that is recovered and recycled to the first step. The enzyme used is *Candida Antarctica* B that is immobilised on an acrylic epoxide resin. The resolution is carried out in the presence of pyrazine that improves the *ee* from 96% when it not used to >99% when it is.

Scheme 15




The patent also gives a number of examples of reacting **45** with alternative chloroformates to give the corresponding carbonates. Examples include the chloroformates isopropenyl, *p*-nitrophenyl and 2-chloroethyl. The patent does provide NMR and IR data for the new compounds.

## Advantages

The process provides an efficient method of preparing the active isomer of this widely used drug.

## Patent No. U.S. 6.969,768

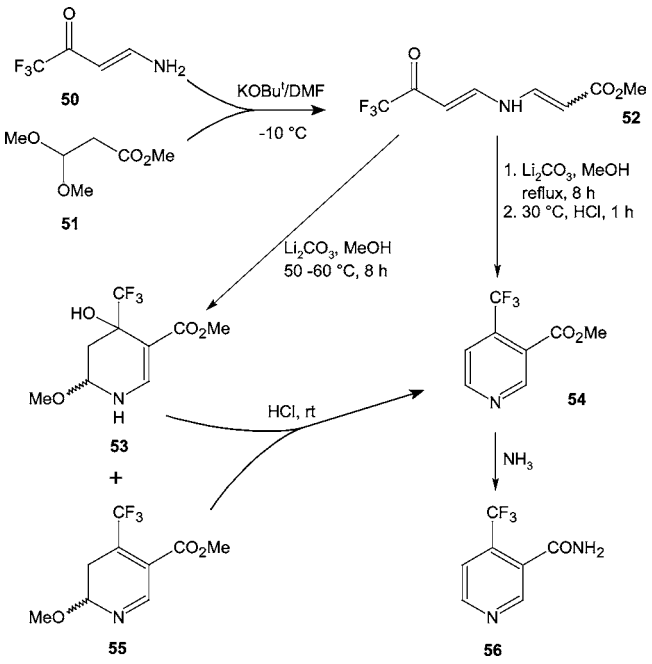
***Assignee: Bayer CropScience GmbH, Frankfurt, Germany***

***Title or Subject: Preparation of 4-Haloalkylnicotinic Acid Derivatives***

The compounds of interest in this patent are the amides such as **56** that can be used to prepare pesticides. **56** can be prepared from the corresponding acid that is formed by a

NaOMe catalysed ring closure of **52**. The patent discloses an improved process for preparing **56** via the ester **54** and the route to prepare **54** is shown in Scheme 16. The first step is treatment of amine **50** with strong base and then condensation with the ester **51** to give the acrylate **52** as a mixture of stereoisomers. The next step is the formation of **54** from **52** via a base-catalyzed ring closure reaction using $Li_2CO_3$. Previous processes use NaOMe but it has been found that $Li_2CO_3$ is very effective. The formation of **54** proceeds via **53** and **55** that are formed as a mixture of isomers. It is shown that **53** can be isolated and then converted to **54** by treatment with HCl. The isomers of **53** are separated by chromatography and $^1H$ and $^{19}F$ NMR data are given for both isomers. The direct conversion of **52** to **54** can be carried out without isolation of **53** or **55** by adding the HCl to the reaction mixture after the initial base-catalyzed reaction.

Scheme 16




The patent also mentions that the ester **54** can be converted to the amide **56** using $NH_3$, but no details are given.

## Advantages

This process provides an efficient new method of producing the ester **54** and also produces novel intermediates.

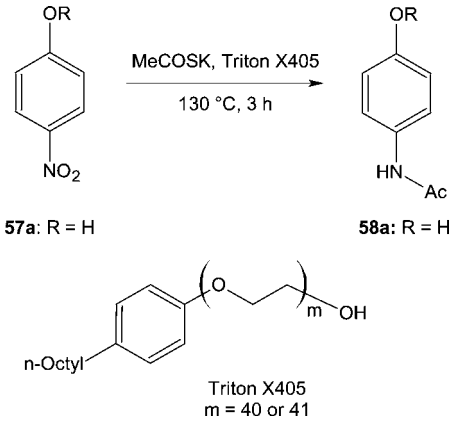
## Patent No. U.S. 6,969,775

***Assignee: The Texas A&M University System, College Station, Texas, U.S.A.***

***Title or Subject: Method of Producing Organic Compounds in the Presence of Oxyethylene Ether Catalyst with Minimal Solvent***

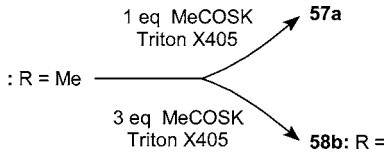
The rather grandiose title of this patent seems to cover everything, but in fact the claims only cover the production of **58a**. The patent is aimed at carrying out reactions in solvent-free systems or with minimum amount of solvents, especially volatile compounds. Although the patent specifically claims a process to prepare **58a**, it does give some details of a number of other reactions using the same technique. The process to prepare **58a** is claimed to be the shortest synthesis known to date and is shown in Scheme 17 and comprises a combined amidation and reduction reaction of **57a**. This is carried out by treating **57a** with MeCOSK at 130 °C in water-free Triton X-405, a nonionic surfactant that is an octylphenoxy poly(ethylene glycol). The patent suggests that the oxyethylene ether functions as a cocatalyst by complexing and solubilising the metal ion rather like crown ethers.

Scheme 17



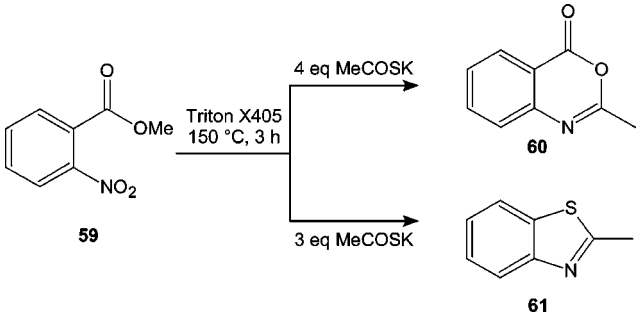

An interesting comparison of using different amounts of MeCOSK in the reaction of **57b** using Triton X-405 is shown in Scheme 18. If one equivalent of the salt is used, the reaction gives **57a** by cleavage of the OMe group. However, if three equivalents are used, the product is **58b** in which the OMe group is unaffected.

Scheme 18




The use of Triton X-405 and the MeCOSK salt is also applied to a range of other compounds. No detailed examples are given, but these are mentioned in the patent. For example, Scheme 19 shows that oxazinone **60** can be prepared as the major product from **59** by using 4 equiv of MeCOSK. If only three equivalents of the salt are used, then the product is **61**, and **60** is not formed.

Scheme 19



The patent does not mention anything about the type of mixing used in this reaction other than to say the reactants are mixed. Mixing and mixers are often overlooked as variables in laboratory reactions. The Triton is a fairly viscous material, and it will not be easy to mix the reagents at ambient conditions; thus, it is quite likely that the reaction rate is going to be affected by mixing. Hence, high temperatures may be needed to reduce the viscosity and allow the reactants to be mixed effectively.

### Advantages

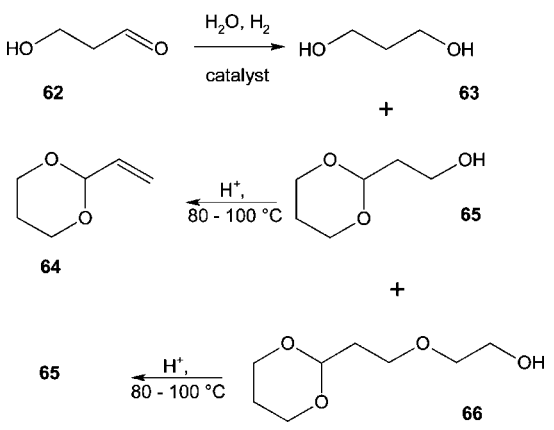
This process removes the need for solvents and provides a novel method of carrying out some potentially synthetically useful reactions.

## Patents No. U.S. 6,969,779 and U.S. 6,972,346

### *Assignee: Shell Oil Company, Houston, Texas, U.S.A.*
### *Title or Subject: Production and Purification of 1,3-Propanediol from 3-Hydroxypropanal*

These two patents cover the production of **63** from **62** and the removal of two acetal impurities **65** and **66**. The hydrogenation of **62** is catalysed by a number of platinum group metals in aqueous solution and produces several impurities including the acetals **65** and **66** (Scheme 20). The product **63** is usually purified by distillation, and although the impurities have lower boiling points than the desired product **63** the product can sometimes contain high levels of **66**. Thus, to improve the purification of **63** by distillation the patent describes a method of converting the acetals to lower-boiling materials that can be more easily removed. The first patent is directed mainly at the removal of **66** and the second at the removal of **65**. The procedure in both patents is to use an acid catalyst to convert **65** or **66** to more volatile components that can be distilled from **63**. Acidic zeolites or ion-exchange resins (IER) are used in both cases to convert the acetals, although the IER is more active so that a lower temperature can be used. The reaction also takes place using mineral acids, but the solid acids are preferred. In the case of **66** the reaction actually produces **65** plus $CH_3CHO$. The acetal **65** is converted to **64** that is more volatile than **65** and easily distilled from the mixture. All decomposition reactions produce water, and this is easily separated by distillation from the product.

Scheme 20




The examples describe the use of 0.6-m diameter distillation columns, indicating that the process has been carried out on a substantial scale.

### Advantages

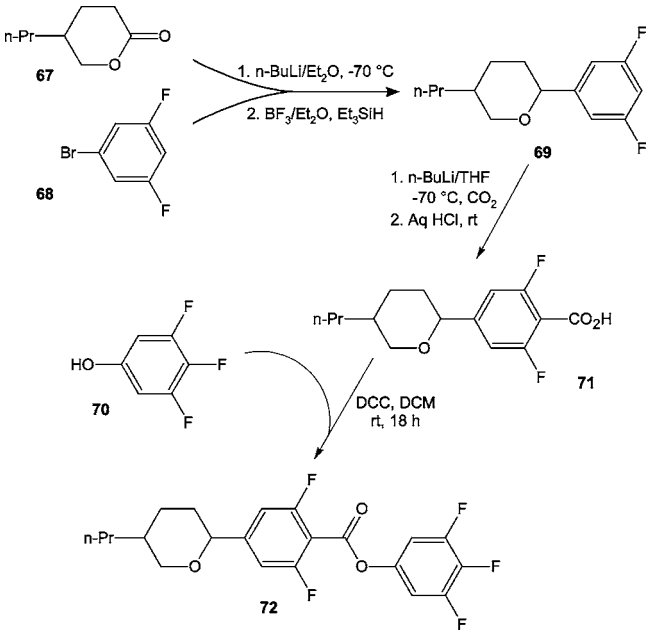
The process provides a simple procedure for purifying the desired product by making use of the ready decomposition of the by-products into volatile compounds.

## Patent No. U.S. 6,974,607

### *Assignee: Merck Patent GmbH, Darmstadt, Germany*
### *Title or Subject: Tetrahydropyrans as Liquid Crystals*

The development of liquid crystal (LC) compounds has increased the availability of flat screen televisions, high definition computer monitors, and mobile phone screens. This has been possible because these new compounds have very high dielectric anisotropy requiring very low voltages to achieve the rapid responses necessary in such screens. This patent describes a range of compounds, such as **72**, that fulfill these requirements and also have good solubility for other components that are used in the production of LC displays. Scheme 21 shows the route used to prepare **72** starting with the condensation of **67** and **68** to give **69** in 62% yield. The next stage is the reaction of **69** with $CO_2$ followed by acidification to give the acid **71** in 82% yield. The final stage is esterification of **71** with **70** in the presence of DCC to give **72** in 78% yield.

Scheme 21




The same procedure was also used to prepare a range of analogous tetrahydropyran compounds that all contained the trifluorophenyl moiety.

### Advantages

The process gives a method of producing liquid crystal materials that have the desired properties of good solubilisation and anisotropy as well as being synthesised in high yields using conventional methods and materials.

## Patent No. U.S. 6,979,735

***Assignee: DSM N. V., Heerlen, Netherlands***

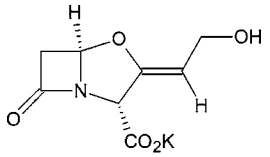
***Title or Subject: Agglomerates by Crystallisation***

The title of this patent may be thought of as an undesirable problem that one tries to avoid in most crystallisation processes. However, in this case the agglomerates are $\beta$-lactams that are desirable since they are more useful for the formulation of antibiotic drugs, especially as tablets. The focus of this patent is the preparation of **73** that is available as augmentin. The agglomerates of **73** are prepared by the following series of steps:

(i) dissolve or suspend **73** in aqueous $Me_2CO$

(ii) add an antisolvent such as EtOAc to the mixture by using a nozzle spray while stirring with a turbine or high shear mixer

This precipitates needle crystals that can be collected. The claims specifically exclude rosette-type crystals, presumably because of potential infringement with other patents. The method is also extended to the production of formulations containing **73** with other antibiotics such as amoxicillin.




**73**

This process shows the importance of mixing and in this case how it can affect the physical form of the product.

### Advantages

The process provides a simple method of producing the desirable physical form of an important drug.

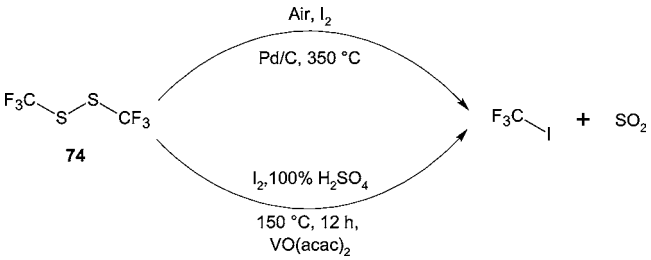
## Patent No. U.S. 6,977,316

***Assignee: Honeywell International Inc., Morristown, New Jersey, U.S.A.***

***Title or Subject: Direct One-Step Synthesis of $CF_3I$***

The compound $CF_3I$ has synthetic uses, but the interest in this patent is that it can be used as a refrigerant and has almost zero ozone-depletion potential. Thus, it is an environmentally friendly replacement for CFCs and hydrochlorofluorocarbons. Previous methods for the preparation of $CF_3I$ involve several steps and use expensive reagents. There are two methods described, and one is gas phase whereas the second is liquid phase (Scheme 22). This shows that the starting material is the disulphide **74**, but it is claimed that $CF_3SH$, $CF_3Ph$, and $CF_3SiMe_3$ can be used. A variety of other metal catalysts are said to be suitable, with Pd/C being preferred. The conversion in the liquid-phase process is about 80%, but no data are given for the gas-phase reaction.

Scheme 22




### Advantages

If the $CF_3I$ is indeed an environmentally friendly refrigerant, then this process may have potential. However, there is no indication whether the preparation of the starting materials is easy and environmentally friendly.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